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B616 B64Y B640 B646 B65X B65Y B650 B652  
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(58) Field of search

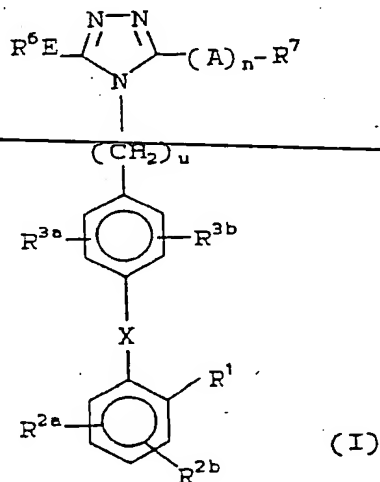
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(54) Substituted triazoles as neurotensin antagonists

(57) Substituted triazoles of the formula (I) as disclosed in EP-0409332-A2, are as neurotensin antagonists useful in the treatment of certain CNS and GI disorders.



(I)

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TITLE OF THE INVENTION

SUBSTITUTED TRIAZOLES AS NEUROTENSIN ANTAGONISTS

15 INTRODUCTION OF THE INVENTION

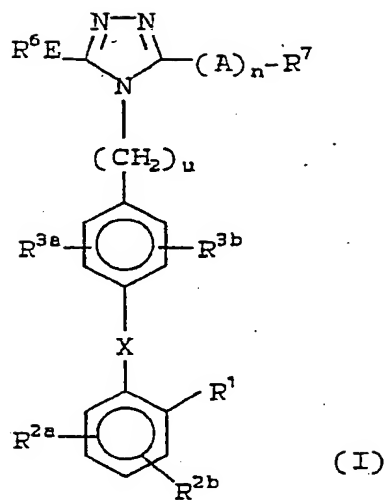
This invention is concerned with a method of treating disease states mediated by neurotensin by the administration to a patient in need of treatment of a therapeutically effective amount of a

20 neurotensin antagonist which is a substituted triazole of structural formula I:

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As neurotensin antagonists these compounds find utility in the treatment of CNS dysfunctions such as psychoses, depression, cognitive dysfunction, such as Alzheimer's disease, anxiety, tardive dyskinesia, drug dependency, panic attack and mania.

5 The neurotensin antagonist property also imparts to the compounds utility in GI disorders such as gastroesophageal reflux disorder (GERD), irritable bowel syndrome, diarrhea, cholic, ulcer, GI tumors, dyspepsia, pancreatitis, esophagitis and

10 gastroparesis. The known ability of neurotensin to release mast cell histamine indicates that antagonists will be useful in the treatment of allergic and inflammatory conditions.

15 BACKGROUND OF THE INVENTION

Neurotensin (NT) is a tridecapeptide hormone (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-OH), originally isolated from the bovine hypothalamus [Carraway, R. and Leeman, S. E., J. Biol. Chem., 248, 6854 (1973)], has subsequently been

20 shown to be distributed in the brain [Uhl, G. R., et al., Proc. Natl. Acad. Sci. USA, 74, 4059-4063 (1977), gastrointestinal tract [1]. Kitabgi, P., Carraway, R. and Leeman, S. E., J. Biol. Chem., 251, 7053 (1976); 2). Carraway, R., Kitabgi, P., and

25 Leeman, S. E., J. Biol. Chem., 253, 7996 (1978); 3). Helmstadler, V., Taugner, C., Feurle, G. E. and Frossman, W. G., Histochemistry, 53, 35-41 (1977)] and pancreas [Feurle, G. E. and Niestroj, S.,

30 Pancreas, 6, 202-207 (1991) and references cited therein] of various animals including human [Mai, J. K., et al., Neuroscience, 22, 499-524 (1987)]. Although the physiological role of neurotensin has

not yet been clearly understood, this endogenous peptide participates in a wide spectrum of central [1). Prange, A. J. and Nemeroff, C. B., Annal. NY Acad. Sciences, 400, 368-375 (1982); 2). Stowe, Z. N. and Nemeroff, C. B., Life Sci., 49, 987-1002, (1991); 3) Kitabgi, P., Neurochem. Int., 14, 111-119 (1989); 4). Levant and Nemeroff, C. B., Current topics in Neuroendocrinology, 8, 231-262 (1988)] and peripheral [Leeman, S. E., Aronin, N. and Ferris, C., Hormone Res., 38, 93-132 (1982)] biological functions.

Neurotensin is also known to release mast cell histamine, indicating that antagonists will be useful in the treatment of allergic and inflammatory conditions, as well. [See, Rossei, S.S. and Miller, R.J., Life Sci., 31, 509-516 (1982) and Kurose, M. and Saeki, K., Eur. J. Pharmacol., 76, 129-136 (1981).]

Neurotensin, like most other peptides, is unable to cross the blood-brain barrier (BBB). However, certain peripheral effects of neurotensin have been observed after central administration of the peptide [Prange, A. J. and Nemeroff, C. B., Annal. NY Acad. Sciences, 400, 368-391 (1982). The direct application of neurotensin into the brain causes hypothermia, potentiation of barbiturate induced sedation, catalepsy, antinociception, blockade of psychostimulant-induced locomotor activity and reduced food consumption. In the central nervous system (CNS), neurotensin behaves as a neurotransmitter or neuromodulator [1) Uhl, G. R. and Snyder, S. H., Eur. J. Pharmacol., 41, 89-91 (1977); 2) Uhl, G. R., Annal. NY Acad. Sciences, 400,

132-149 (1982)], and has been shown to have close anatomical and biochemical associations with the dopaminergic (DA) system [Nemeroff, C. B., et al. Annal. NY Acad. Sciences, 400, 330-344 (1982)].

5 Neurotensin increases the synthesis and the turnover of DA in rat brain. Acute and chronic treatment with clinically efficacious antipsychotic drugs (e.g., haloperidol, chlorpromazine) have consistently demonstrated an increase in neurotensin concentrations in the nucleus accumbens and striatum  
10 while phenothiazines that are not antipsychotics did not produce this increase. Behaviorally, neurotensin, after central administration, mimics the effects of systemically administered neuroleptics. However, unlike classical neuroleptics (which primarily acts  
15 on D<sub>2</sub> receptors), neurotensin fails to bind to dopamine receptors or inhibit cAMP accumulation following DA receptor activation. Neurotensin does not block the stereotypy induced by DA agonists. The post-mortem studies of patients with schizophrenia  
20 showed an increase in the level of neurotensin in the Brodman's area 32 of human brain [Nemeroff, C. B., et. al., Science, 221, 972-975 (1983) and references cited therein], which suggest possible roles of  
~~neurotensin in the pathophysiology of this disease.~~

25 Neurotensin receptors have also been implicated in Parkinson's disease and progressive supranuclear palsy [Chinaglia, G. et al., Neuroscience, 39, 351-360 (1990)].

30 Of the total body neurotensin in many mammalian species, more than 80% is present in the gastrointestinal tract, especially in the distal small intestine in the endocrine like N-cells. In the

gut, neurotensin stimulates pancreatic secretion [Sakamoto, T., et al, Surgery, 96, 146-53 (1984)], inhibits gastric acid secretion and gastric emptying [Blackburn, A. M., Lancet, 1, 987-989 (1980)]. Neurotensin also stimulates the growth of small  
5 intestinal mucosa in an isolated defunctional loop of jejunum, which suggests a direct systemic effect of neurotensin in the gut. In addition, neurotensin can stimulate pancreatic exocrine secretion in mammals [Iwatsuki, K., et al., Clin. Expt. Pharmacol.  
10 Physiol., 18, 475-481 (1991) and references cited therein].

From the structural work, it is evident that the biological activity of neurotensin resides within the carboxy terminal five or six amino acid residues.  
15 The C-terminal hexapeptide NT<sup>8-13</sup> has displayed full biological activity of the tridecapeptide. In contrast, all amino terminal partial sequences are essentially inactive [Leeman, S. E. and Carraway, R. E., Annal. NY Acad. Sciences, 400, 1-16 (1982)]. The  
20 C-terminal COOH group and two Arg residues are essential for the biological activity of NT<sup>8-13</sup> as well as neurotensin. L-amino acids are required at positions-9,10,11 and 13, and only Arg<sup>8</sup> can be  
replaced by D-Arg without loss of any activity. At  
25 the position-11, an aromatic amino acid is essential. Similarly, alkyl side-chains of Ile<sup>12</sup> and Leu<sup>13</sup> are also necessary for full biological activity [Kitabgi, P., Annal. NY Acad. Sciences, 400, 37-53 (1982)].  
Most of the analogues of neurotensin examined  
30 generally behaved as agonists. However, two analogues D-Trp<sup>11</sup>-NT and Tyr(Me)<sup>11</sup>-NT have displayed partial antagonist activity [Rioux, F. R., et al., Eur. J. Pharmacol., 66, 373-379 (1980)].

The compounds useful in the novel method of treatment of this invention are known in the art having been published in European Patent Application EP 409,332 (Merck & Co., Inc.) where they are alleged to be angiotensin-II (A-II) receptor antagonists useful in the treatment of hypertension, ocular hypertension.

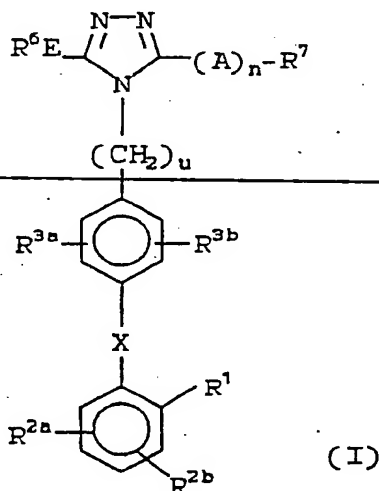
Although there are reports of peptidic neurotensin antagonists, they are unstable and not orally active and none are clinically available.

There are no reports of non-peptidic neurotensin antagonists.

Now with this invention, there are provided non-peptidic neurotensin antagonists.

#### DETAILED DESCRIPTION OF THE INVENTION

This compounds useful in the novel method of treatment of this invention have structural formula I:



pharmaceutically acceptable salt thereof



wherein:

R<sup>1</sup> is

- (a) -NHSO<sub>2</sub>R<sup>23</sup>,
- (b) -NHSO<sub>2</sub>NHCOR<sup>23</sup>,
- (c) -NHCONHSO<sub>2</sub>R<sup>23</sup>,
- 5 (d) -SO<sub>2</sub>NHR<sup>23</sup>,
- (e) -SO<sub>2</sub>-NHCOR<sup>23</sup>,
- (f) -SO<sub>2</sub>NHCONR<sup>9</sup>R<sup>23</sup>
- (g) -SO<sub>2</sub>NHCOOR<sup>23</sup>
- (h) -SO<sub>2</sub>NHOR<sup>23</sup>,
- 10 (i) -CH<sub>2</sub>SO<sub>2</sub>NHCOR<sup>23</sup>,
- (j) -CH<sub>2</sub>SO<sub>2</sub>NHCOR<sup>23</sup>,
- (k) -CO<sub>2</sub>H, or
- (l) -1H-tetrazol-5-yl;

15 R<sup>2a</sup> and R<sup>2b</sup> are each independently:

- (a) hydrogen,
- (b) Cl, Br, I, F,
- (c) CF<sub>3</sub>,
- (d) C<sub>1</sub>-C<sub>4</sub>-alkyl,
- 20 (e) C<sub>1</sub>-C<sub>4</sub>-alkoxy; or

R<sup>3a</sup> is

- (a) H,
- (b) Cl, Br, I, F,
- 25 (c) C<sub>1</sub>-C<sub>6</sub>-alkyl,
- (d) C<sub>1</sub>-C<sub>6</sub>-alkoxy,
- (e) C<sub>1</sub>-C<sub>6</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl;

R<sup>3b</sup> is

- 30 (a) H,
- (b) Cl, Br, I, F,
- (c) C<sub>1</sub>-C<sub>6</sub>-alkyl,

- (d) C<sub>3</sub>-C<sub>6</sub>-cycloalkyl,  
(e) C<sub>1</sub>-C<sub>6</sub>-alkoxy, or  
(f) CF<sub>3</sub>;

R<sup>4</sup> is H, C<sub>1</sub>-C<sub>6</sub>-alkyl, benzyl or phenyl;

5

R<sup>5</sup> is H,  $\begin{array}{c} \text{R}^4 \\ | \\ \text{CH-O-C} \\ || \\ \text{O} \end{array}$ -R<sup>4</sup>;

10

E is a single bond, -NR<sup>13</sup>(CH<sub>2</sub>)<sub>s</sub>-, -S(O)<sub>x</sub>(CH<sub>2</sub>)<sub>s</sub>-  
where x is 0 to 2 and s is 0 to 5, -CH(OH)-,  
-O(CH<sub>2</sub>)<sub>s</sub>-, -CO-;

R<sup>6</sup> is

15

(a) aryl wherein aryl is defined as phenyl or  
naphthyl which can be unsubstituted or  
substituted with 1 or 2 substituents  
selected from the group consisting of Cl,  
Br, I, F, -O-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyl, -NO<sub>2</sub>,  
-CF<sub>3</sub>, -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, -S-C<sub>1</sub>-C<sub>4</sub>-alkyl, -OH, -NH<sub>2</sub>,  
C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, and C<sub>2</sub>-C<sub>10</sub>-alkenyl;

20

(b) C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl  
each of which can be unsubstituted  
substituted with a substituent selected from  
the group consisting of aryl, C<sub>3</sub>-C<sub>7</sub>-

25

cycloalkyl, Cl, Br, I, F, -OH,  
-O-C<sub>1</sub>-C<sub>4</sub>-alkyl, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub>-alkyl),  
-N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, -NH-SO<sub>2</sub>R<sup>4</sup>, -COOR<sup>4</sup>,  
-SO<sub>2</sub>NHR<sup>9</sup>, -S-C<sub>1</sub>-C<sub>4</sub>-alkyl; or

30

(c) an unsubstituted, monosubstituted or  
disubstituted aromatic 5 or 6 membered  
heterocycle which contains one or two  
heteroatoms selected from the group

consisting of N, O and S, and wherein the substituents are members selected from the group consisting of -OH, -SH, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyloxy, -CF<sub>3</sub>, Cl, Br, I, F, or NO<sub>2</sub>;

(d) mono-, di-, tri- or perfluoro-C<sub>1</sub>-C<sub>5</sub>-alkyl;

5 (e) C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, unsubstituted or substituted with one or more substituents selected from the group consisting of C<sub>1</sub>-C<sub>4</sub>-alkyl, -O-C<sub>1</sub>-C<sub>4</sub>-alkyl, -S-C<sub>1</sub>-C<sub>4</sub>-alkyl, -OH, perfluoro-C<sub>1</sub>-C<sub>4</sub>-alkyl, or Cl, Br, F, I;

10 (f) C<sub>3</sub>-C<sub>7</sub>-cycloalkyl-C<sub>1</sub>-C<sub>3</sub>-alkyl wherein the cycloalkyl is substituted as in (e) above,

A is S(O)<sub>p</sub>, -O- NHC(=O)-, -C(=O)NR<sup>13</sup>-, or -NR<sup>13</sup>-, wherein p is 0 to 2;

15

R<sup>7</sup> is

(a) C<sub>1</sub>-C<sub>10</sub>-alkyl,

(b) substituted C<sub>1</sub>-C<sub>10</sub> alkyl in which one or more substituent(s) is selected from

20

(1) Cl, Br, I, F,

(2) hydroxy,

(3) C<sub>1</sub>-C<sub>10</sub>-alkoxy,

(4) C<sub>1</sub>-C<sub>5</sub>-alkoxycarbonyl,

(5) C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyloxy,

25

(6) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,

(7) phenyl,

(8) substituted phenyl in which the substituents are V and W,

(9) C<sub>1</sub>-C<sub>10</sub>-alkyl-S(O)<sub>p</sub>,

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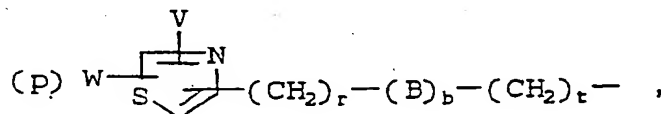
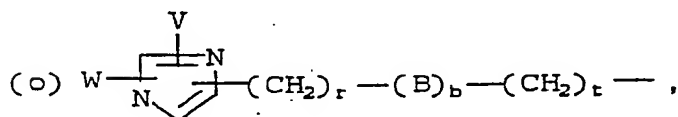
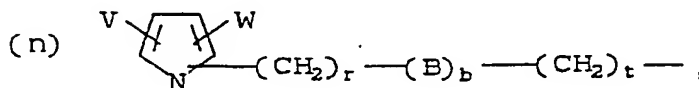
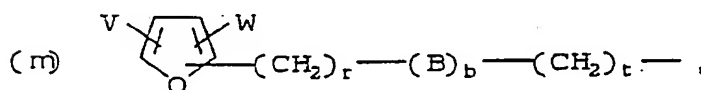
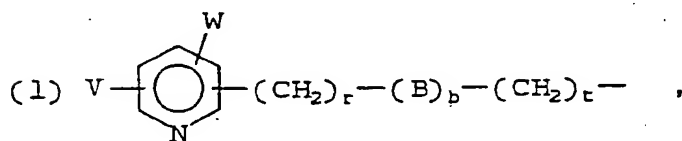
(10) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-S(O)<sub>p</sub>,

(11) phenyl-S(O)<sub>p</sub>.

- (12) substituted phenyl-S(O)<sub>p</sub> in which the substituents are V and W,  
(13) oxo,  
(14) carboxy,  
(15) NR<sup>9</sup>R<sup>10</sup>,  
5 (16) C<sub>1</sub>-C<sub>5</sub>-alkylaminocarbonyl,  
(17) di(C<sub>1</sub>-C<sub>5</sub>-alkyl)aminocarbonyl,  
(18) cyano;  
(c) perfluoro-C<sub>1</sub>-C<sub>4</sub>-alkyl,  
(d) C<sub>2</sub>-C<sub>10</sub>-alkenyl,  
10 (e) C<sub>2</sub>-C<sub>10</sub>-alkynyl,  
(f) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,  
(g) substituted C<sub>3</sub>-C<sub>8</sub>-cycloalkyl in which one or more substituent(s) is selected from the group:  
15 (1) I, Br, Cl, F,  
(2) hydroxy,  
(3) C<sub>1</sub>-C<sub>10</sub>-alkoxy,  
(4) C<sub>1</sub>-C<sub>5</sub>-alkoxycarbonyl,  
(5) C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyloxy,  
20 (6) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,  
(7) phenyl,  
(8) substituted phenyl in which the substituents are V and W,  
(9) C<sub>1</sub>-C<sub>10</sub>-alkyl-S(O)<sub>p</sub> in which p is 0 to 2,  
25 (10) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-S(O)<sub>p</sub>,  
(11) phenyl-S(O)<sub>p</sub>,  
(12) substituted phenyl-S(O)<sub>p</sub> in which the substituents are V and W,  
(13) oxo,  
30 (14) carboxy,  
(15) NR<sup>9</sup>R<sup>10</sup>,  
(16) C<sub>1</sub>-C<sub>5</sub>-alkylaminocarbonyl;  
(17) di(C<sub>1</sub>-C<sub>5</sub>-alkyl)aminocarbonyl;

- (18) cyano,  
 (19)  $C_1-C_4$ -alkylcarbonyl,  
 (20)  $(C_1-C_5)$ -alkyl,

- (h) phenyl,  
 (i) substituted phenyl in which the substituents  
 are V and W,  
 (j) phenyl- $(CH_2)_r-(B)_b-(CH_2)_t-$   
 (k) substituted phenyl- $(CH_2)_r-(B)_b-(CH_2)_t-$  in  
 which the phenyl group is substituted with V  
 and W;



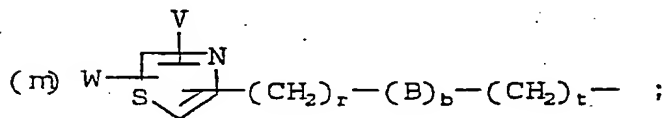
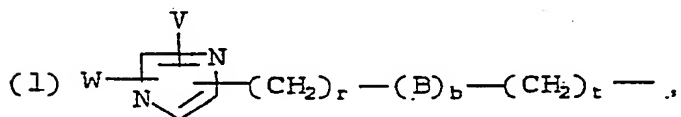
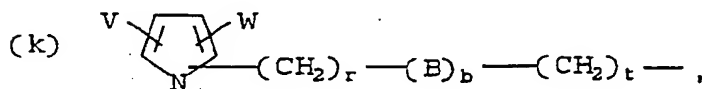
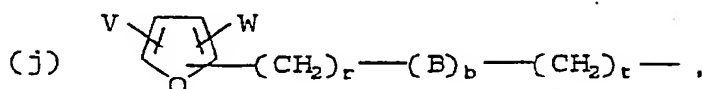
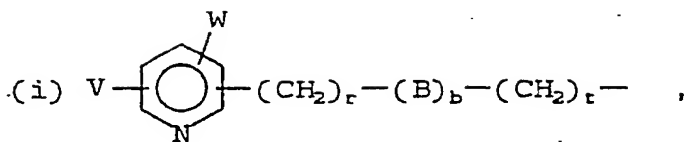
with the proviso that when E is a single bond and n  
 is 0, then  $R^7$  is:

- (a) substituted  $C_1-C_{10}$ -alkyl in which one or  
 more substituent(s) is selected from:  
 (1)  $C_3-C_8$ -cycloalkyl,  
 (2) phenyl,

- (3) substituted phenyl as defined above in which the substituents are V and W,  
(4)  $C_3-C_8$ -cycloalkyl-S(O)<sub>p</sub> where p is 0 to 2,  
(5) phenyl-S(O)<sub>p</sub> where p is 0 to 2,  
5 (6) substituted phenyl-S(O)<sub>p</sub> where p is 0 to 2 and the substituents are V and W;  
(b) CF<sub>3</sub>;  
(c)  $C_3-C_8$ -cycloalkyl;  
(d) substituted  $C_3-C_8$ -cycloalkyl in which the  
10 substituent is selected from:  
(1)  $C_1-C_5$ -alkyl,  
(2)  $C_1-C_5$ -alkoxy;  
(e) phenyl,  
(f) substituted phenyl in which the substituents  
15 are V and W;  
(g) phenyl-(CH<sub>2</sub>)<sub>r</sub>-(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>- in which b is 0 when B is -C(O)-;  
(h) substituted phenyl-(CH<sub>2</sub>)<sub>r</sub>-(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>- in  
20 which b is 0 when B is -C(O)- and the phenyl group is substituted with V and W;

25

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n is 0 or 1;

B is  $-C(O)-$ ,  $-S-$ ,  $-O-$ ,  $-NR^4$ ,  $-NR^4C(O)-$ , or  $-C(O)NR^4$ ;

b is 0 or 1;

r and t are 0 to 2;

u is 1 or 2;

p is 0 to 2;

V and W are each independently selected from:

- (a) H,
  - (b) C<sub>1</sub>-C<sub>5</sub>-alkoxy,
  - (c) C<sub>1</sub>-C<sub>5</sub>-alkyl,
  - (d) hydroxy,
  - 5 (e) C<sub>1</sub>-C<sub>5</sub>-alkyl-S(O)<sub>p</sub>,
  - (f) -CN,
  - (g) -NO<sub>2</sub>,
  - (h) -NR<sup>9</sup>R<sup>10</sup>,
  - (i) C<sub>1</sub>-C<sub>4</sub>-alkyl-CONR<sup>9</sup>R<sup>10</sup>,
  - 10 (j) -CO<sub>2</sub>R<sup>9</sup>,
  - (k) C<sub>1</sub>-C<sub>5</sub>-alkyl-carbonyl,
  - (l) trifluoromethyl,
  - (m) Cl, Br, I, F,
  - (n) hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl-,
  - 15 (o) C<sub>1</sub>-C<sub>4</sub>-alkyl-CO<sub>2</sub>R<sup>9</sup>,
  - (p) -1H-tetrazol-5-yl,
  - (q) -NH-SO<sub>2</sub>CF<sub>3</sub>;
  - (r) aryl,
  - (s) -OCONR<sup>9</sup>R<sup>10</sup>,
  - 20 (t) -NR<sup>4</sup>CO<sub>2</sub>R<sup>9</sup>,
  - (u) -NR<sup>4</sup>CONR<sup>9</sup>R<sup>10</sup>,
  - (v) -NR<sup>4</sup>CON(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>Q where Q is O, S(O)<sub>p</sub> or NR<sup>9</sup>,
  - (w) -OCON(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>Q, or
  - (x) -CONR<sup>9</sup>R<sup>10</sup>;
- 

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R<sup>9</sup> is H, C<sub>1</sub>-C<sub>5</sub>-alkyl, phenyl or benzyl;

R<sup>10</sup> is H, C<sub>1</sub>-C<sub>4</sub>-alkyl;

30 or R<sup>9</sup> and R<sup>10</sup> together may be -(CH<sub>2</sub>)<sub>m</sub>- where m is 3-6;



R<sup>11</sup> is H, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>4</sub>-alkenyl,  
C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, or -CH<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>R<sup>20</sup>;

R<sup>12</sup> is -CN, -NO<sub>2</sub> or -CO<sub>2</sub>R<sup>4</sup>;

5 R<sup>13</sup> is H, C<sub>1</sub>-C<sub>4</sub>-acyl, C<sub>1</sub>-C<sub>6</sub>-alkyl, allyl,  
C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, phenyl or benzyl;

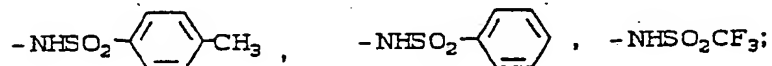
R<sup>14</sup> is H, C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-perfluoroalkyl,  
C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, phenyl or benzyl;

10 R<sup>15</sup> is H, C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxy;

R<sup>16</sup> is H, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, phenyl or  
benzyl;

15 R<sup>17</sup> is -NR<sup>9</sup>R<sup>10</sup>, -OR<sup>10</sup>, -NHCONH<sub>2</sub>, -NHCSNH<sub>2</sub>,

20



25

R<sup>18</sup> and R<sup>19</sup> are independently C<sub>1</sub>-C<sub>4</sub>-alkyl or taken  
together are -(CH<sub>2</sub>)<sub>q</sub> where q is 2 or 3;

30

R<sup>20</sup> is H, -NO<sub>2</sub>, -NH<sub>2</sub>, -OH or -OCH<sub>3</sub>;

R<sup>21</sup> is C<sub>1</sub>-C<sub>5</sub>-alkyl or CF<sub>3</sub>;

R<sup>22</sup> is

- 5 (a) phenyl, unsubstituted or substituted with 1  
or 2 substituents selected from the group  
consisting of: Cl, Br, I, or F, -O-C<sub>1</sub>-C<sub>4</sub>-  
alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyl, -NO<sub>2</sub>, -CF<sub>3</sub>, -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>,  
-S-C<sub>1</sub>-C<sub>4</sub>-alkyl, -OH, -NH<sub>2</sub>, -COOR<sup>4</sup>,  
10 C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, and C<sub>3</sub>-C<sub>10</sub>-alkenyl;  
(b) C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl  
each of which is unsubstituted or  
substituted with one or more substituents  
selected from the group consisting of aryl,  
15 C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, Cl, Br, I, F, -OH,  
-O-C<sub>1</sub>-C<sub>4</sub>-alkyl, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub>-alkyl),  
-N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, -NH-SO<sub>2</sub>R<sup>4</sup>, -COOR<sup>4</sup>,  
-SO<sub>2</sub>NHR<sup>9</sup>, and -S-C<sub>1</sub>-C<sub>4</sub>-alkyl;  
(c) an unsubstituted, monosubstituted or  
20 disubstituted aromatic 5 or 6 membered ring  
comprising one or two heteroatoms selected  
from the group consisting of N, O, and S,  
and wherein the substituents are members  
selected from the group consisting of: -OH,  
25 -SH, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyloxy, -CF<sub>3</sub>,  
-COOR<sup>4</sup>, Cl, Br, I, F, and NO<sub>2</sub>; or  
(d) C<sub>3</sub>-C<sub>7</sub>-cycloalkyl unsubstituted or  
substituted with one or more substituents  
selected from the group consisting of:  
30

C<sub>1</sub>-C<sub>4</sub>-alkyl, -O-C<sub>1</sub>-C<sub>4</sub>-alkyl, -S-C<sub>1</sub>-C<sub>4</sub>-alkyl,  
-OH, -COOR<sup>4</sup>, C<sub>1</sub>-C<sub>4</sub>-perfluoroalkyl, Cl, Br,  
F, and I, or

(e) (C<sub>1</sub>-C<sub>4</sub>)-perfluoroalkyl;

5 R<sup>23</sup> is

(a) aryl,

(b) heteroaryl,

(c) C<sub>3</sub>-C<sub>7</sub>-cycloalkyl,

10 (d) C<sub>1</sub>-C<sub>4</sub>-alkyl, unsubstituted or substituted  
with a substituent selected from the group  
consisting of aryl, heteroaryl as defined  
above, -OH, -SH, C<sub>1</sub>-C<sub>4</sub>-alkyl,

15 -O(C<sub>1</sub>-C<sub>4</sub>-alkyl), -S(C<sub>1</sub>-C<sub>4</sub>-alkyl), -CF<sub>3</sub>, Cl,  
Br, F, I, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub>-alkyl,  
-NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub>-alkyl), -N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>,  
-N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>L where L is a single bond, CH<sub>2</sub>,  
O, S(O)<sub>p</sub> or NR<sup>9</sup>, -PO<sub>3</sub>H,  
-PO(OH)(O-C<sub>1</sub>-C<sub>4</sub>-alkyl);

20 X is

(a) a carbon-carbon single bond,

(b) -CO-,

(c) -O-,

(d) -S-,

25 (e) -N-,  
|  
R<sup>13</sup>

(f) -CON-,  
|  
R<sup>15</sup>

30 (g) -NCO-,  
|  
R<sup>15</sup>

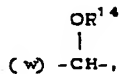
(h) -OCH<sub>2</sub>-,

(i) -CH<sub>2</sub>O-

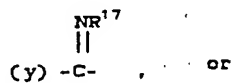
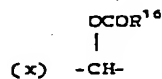
(j) -SCH<sub>2</sub>-,

- (k)  $-\text{CH}_2\text{S}-$ ,  
 (l)  $-\text{NHC}(\text{R}^9)(\text{R}^{10})-$ ,  
 (m)  $-\text{NR}^9\text{SO}_2-$ ,  
 (n)  $-\text{SO}_2\text{NR}^9-$ ,  
 (o)  $-\text{C}(\text{R}^9)(\text{R}^{10})\text{NH}-$ ,  
 5 (p)  $-\text{CH}=\text{CH}-$ ,  
 (q)  $-\text{CF}=\text{CF}-$ ,  
 (r)  $-\text{CH}=\text{CF}-$ ,  
 (s)  $-\text{CF}=\text{CH}-$ ,  
 (t)  $-\text{CH}_2\text{CH}_2-$ ,  
 10 (u)  $-\text{CF}_2\text{CF}_2-$ ,  
 (v) 1,1 and 1,2-disubstituted cyclopropyl,

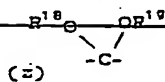
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Z is O, NR<sup>13</sup> or S.

The terms "alkyl", "alkenyl", "alkynyl" and the like include both the straight chain and branched chain species of these generic terms wherein the number of carbon atoms in the species permit. Unless otherwise noted, the specific names for these generic terms shall mean the straight chain species. For example, the term "butyl" shall mean the normal butyl substituent, n-butyl.

One embodiment of the compounds of Formula (I) are those compounds wherein:

- 15 R<sup>1</sup> is
- (a) -SO<sub>2</sub>NHCOR<sup>23</sup>,
  - (b) -SO<sub>2</sub>NHCONR<sup>9</sup>R<sup>23</sup>,
  - (c) -SO<sub>2</sub>NHCOOR<sup>23</sup>,
  - (d) -SO<sub>2</sub>NHOR<sup>23</sup>,
  - 20 (e) -CH<sub>2</sub>SO<sub>2</sub>NHCOR<sup>23</sup>, or
  - (f) -1H-tetrazol-5-yl;

R<sup>2a</sup> is H;

---

25 R<sup>2b</sup> is H, F, Cl, CF<sub>3</sub> or C<sub>1</sub>-C<sub>4</sub>-alkyl;

R<sup>3a</sup> is H;

30 R<sup>3b</sup> is H, F, Cl, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>5</sub>-C<sub>6</sub>-cycloalkyl, -COOCH<sub>3</sub>, -COOC<sub>2</sub>H<sub>5</sub>, -SO<sub>2</sub>-CH<sub>3</sub>, NH<sub>2</sub>, -N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub> or -NH-SO<sub>2</sub>CH<sub>3</sub>;

E is a single bond, -O- or -S-;

R<sup>6</sup> is

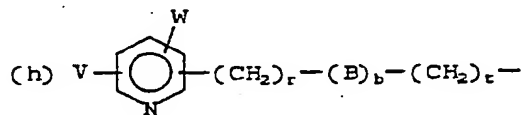
- 5 (a) C<sub>1</sub>-C<sub>6</sub>-alkyl unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF<sub>3</sub>, OH, -O-CH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -S-CH<sub>3</sub>, -S-C<sub>2</sub>H<sub>5</sub> and phenyl;
- (b) C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl;
- 10 (c) aryl either unsubstituted or substituted with a substituent selected from the group consisting of halo (Cl, F, Br, I), -CF<sub>3</sub>, -NO<sub>2</sub>, -OH, -NH<sub>2</sub>, -S-CH<sub>3</sub>, -S-C<sub>2</sub>H<sub>5</sub>, -SO<sub>2</sub>NH<sub>2</sub> and -O-CH<sub>3</sub>;
- (d) a heteroaryl selected from the group consisting of 2-pyridyl, 4-pyridyl,
- 15 2-pyrimidyl, 4-pyrimidyl, imidazolyl, thiazolyl, thienyl, or furyl;
- (e) perfluoro-C<sub>1</sub>-C<sub>4</sub>-alkyl selected from CF<sub>3</sub>, CF<sub>3</sub>CF<sub>2</sub>, CF<sub>3</sub>CF<sub>2</sub>CF<sub>2</sub>, CF<sub>3</sub>CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>;
- 20 (f) C<sub>3</sub>-C<sub>7</sub>-cycloalkyl unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF<sub>3</sub>, OH, -O-CH<sub>3</sub>, -O-C<sub>2</sub>H<sub>5</sub>, -S-CH<sub>3</sub>, -S-C<sub>2</sub>H<sub>5</sub>, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, (CF<sub>2</sub>)<sub>2</sub>CF<sub>3</sub> and phenyl;

25 R<sup>7</sup> is:

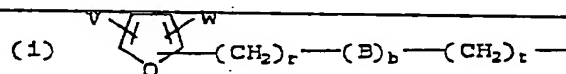
- (a) C<sub>1</sub>-C<sub>10</sub>-alkyl,
- (b) substituted C<sub>1</sub>-C<sub>10</sub>-alkyl in which one or two substituents are selected from:
- 30 (1) hydroxy,
- (2) C<sub>1</sub>-C<sub>5</sub>-alkoxy,
- (3) C<sub>1</sub>-C<sub>5</sub>-alkoxycarbonyl,
- (4) C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyloxy,

- (5) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,  
 (6) phenyl,  
 (7) substituted phenyl in which the  
       substituents are V and W,  
 (8) C<sub>1</sub>-C<sub>5</sub>-alkyl-S(O)<sub>p</sub>,  
 5 (9) phenyl-S(O)<sub>p</sub>,  
 (10) substituted phenyl-S(O)<sub>p</sub> in which the  
       substituents are V and W,  
 (11) oxo,  
 (12) carboxy,  
 10 (13) C<sub>1</sub>-C<sub>5</sub>-alkylaminocarbonyl, or  
 (14) di(C<sub>1</sub>-C<sub>5</sub>-alkyl)aminocarbonyl;  
 (c) CF<sub>3</sub>,  
 (d) phenyl,  
 (e) substituted phenyl in which the substituents  
 15 are V and W,  
 (f) phenyl-(CH<sub>2</sub>)<sub>r</sub>-(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 (g) substituted phenyl-(CH<sub>2</sub>)<sub>r</sub>-(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>-,

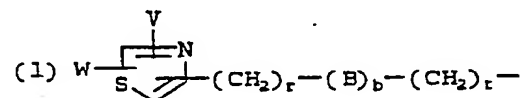
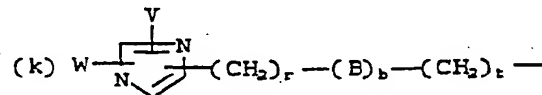
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A is -S-, -S(O)- or -O-;

V and W are independently selected from:

- (a) hydrogen,
- (b) C<sub>1</sub>-C<sub>5</sub>-alkoxy,
- 5 (c) C<sub>1</sub>-C<sub>5</sub>-alkyl,
- (d) hydroxy,
- (e) NR<sup>9</sup>R<sup>10</sup>,
- (f) CO<sub>2</sub>R<sup>9</sup>,
- (g) trifluoromethyl,
- 10 (h) Cl, Br, I, F,
- (i) hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl,
- (j) -1H-tetrazol-5-yl,
- (k) -NH-SO<sub>2</sub>CF<sub>3</sub>,
- (l) -CN,
- 15 (m) -NO<sub>2</sub>,
- (n) C<sub>1</sub>-C<sub>5</sub>-alkyl-S(O)<sub>p</sub>,
- (o) C<sub>1</sub>-C<sub>4</sub>-alkyl-CONR<sup>9</sup>R<sup>10</sup>,
- (p) C<sub>1</sub>-C<sub>5</sub>-alkylcarbonyl, or
- (q) -CONR<sup>9</sup>R<sup>10</sup>;

20

u is 1;

X is:

- 
- (a) ~~carbon-carbon single bond,~~
  - 25 (b) -C(O)-, or
  - (c) -NR<sup>15</sup>C(O)-.

30 In one class of this embodiment are those compounds of formula (I) wherein:

E is a single bond or -S-;



R<sup>2a</sup>, R<sup>2b</sup>, R<sup>3a</sup> and R<sup>3b</sup> are each H;

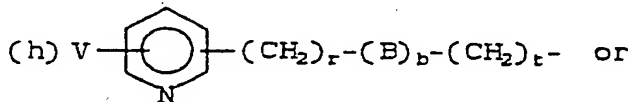
R<sup>6</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl.

5 Illustrating this class are those compounds of  
formula (I) wherein:

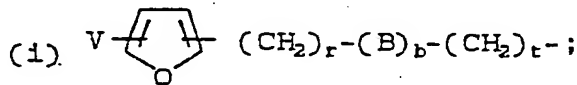
R<sup>7</sup> is:

- (a) C<sub>1</sub>-C<sub>10</sub>-alkyl,
- (b) substituted C<sub>1</sub>-C<sub>10</sub>-alkyl in which one or two  
10 substituents are selected from:
  - (1) hydroxy,
  - (2) C<sub>1</sub>-C<sub>5</sub>-alkoxy,
  - (3) C<sub>1</sub>-C<sub>5</sub>-alkoxycarbonyl,
  - (4) phenyl,
  - 15 (5) carboxy,
  - (6) C<sub>1</sub>-C<sub>5</sub>-alkylaminocarbonyl;
- (c) CF<sub>3</sub>;
- (d) phenyl;
- (e) phenyl substituted with V and W;
- 20 (f) phenyl-(CH<sub>2</sub>)<sub>r</sub>-(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>-;
- (g) phenyl-(CH<sub>2</sub>)<sub>r</sub>-(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>- in which the  
phenyl is substituted with V and W;

25



30



V and W are selected from:

- (a) hydrogen,
- (b) C<sub>1</sub>-C<sub>5</sub>-alkyl,
- (c) C<sub>1</sub>-C<sub>5</sub>-alkoxy,
- (d) CO<sub>2</sub>R<sup>9</sup>,
- 5 (e) halogen,
- (f) hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl,
- (g) -1H-tetrazol-5-yl,
- (h) -NH-SO<sub>2</sub>CF<sub>3</sub>;
- (i) -CN,
- 10 (j) -NO<sub>2</sub>; and

X is -NR<sup>15</sup>C(O)- or a carbon-carbon single bond.

The compounds of Formula (I) can be  
15 synthesized using the reactions and techniques  
described in published European Patent Application  
EP 409,332 (Merck & Co. Inc.) and EP 323,841 (E.I.  
DuPont De Nemours & Co.). The above mentioned  
application discloses the compounds of this invention  
20 where they are alleged to be angiotensin II receptor  
antagonists useful in the treatment of hypertension  
and ocular hypertension.

The reactions are performed in a solvent  
~~appropriate to the reagents and materials~~  
25 employed and suitable for the transformation being  
effected. It is understood by those skilled in the  
art of organic synthesis that the functionality  
present on the heterocycle and in the reactants being  
employed should be consistent with the chemical  
30 transformations being conducted. Depending upon the  
reactions and techniques employed, optimal yields may  
require changing the order of synthetic steps or use  
of protecting groups followed by deprotection.

The compounds useful in the novel method treatment of this invention form salts with various inorganic and organic acids and bases which are also within the scope of the invention. Such salts include ammonium salts, alkali metal salts like sodium and potassium salts, alkaline earth metal salts like the calcium and magnesium salts, salts with organic bases; e.g., dicyclohexylamine salts, N-methyl-D-glucamine, salts with amino acids like arginine, lysine, and the like. Also, salts with organic and inorganic acids may be prepared; e.g., HCl, HBr, H<sub>2</sub>SO<sub>4</sub>, H<sub>3</sub>PO<sub>4</sub>, methanesulfonic, toluenesulfonic, maleic, fumaric, camphorsulfonic.

The salts can be formed by conventional means, such as by reacting the free acid or free base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the cations of an existing salt for another cation on a suitable ion exchange resin.

Neurotensin is a peptide hormone and the assays described below have been developed to identify neurotensin antagonists and to determine their efficacy in vitro. The following three assays have been employed for that purpose.

RAT FOREBRAIN RECEPTOR ASSAY

Male rats are sacrificed by decapitation following ether anesthetization. Forebrains are  
5 homogenized using a polytron in 20 volumes 50 mM Tris HCl, pH 7.4, and centrifuged at 50,000 x g for 20 min. The resulting pellet is washed twice by rehomogenization and centrifugation as before. The final pellet is resuspended at a concentration of 8  
10 mg tissue (wet weight) per 0.750 ml of 50  $\mu$ M Tris HCl, pH 7.4, which also contains 1 mM EDTA, 4  $\mu$ g/ml bacitracin, 5  $\mu$ M levocabastine HCl, 1mM phenanthroline, 10  $\mu$ g/ml soybean trypsin inhibitor and 100  $\mu$ M phenyl methyl sulfonyl fluoride. Assay  
15 tubes (13 X 100 polypropylene) receive 1) 100  $\mu$ l buffer or 10  $\mu$ M neurotensin (for non-specific binding) 2) 100  $\mu$ l of 60 pM [ $^{125}$ I]neurotensin 3) 20  $\mu$ l test compounds 4) 750  $\mu$ l tissue suspension and 5) enough buffer to bring final volume to 1 ml. After  
20 30 minutes at room temp, the samples are filtered using a Brandel M24 cell harvester with GF/B filtermats that have been presoaked in 0.2% polyethyleneimine for 2 hours. The tubes are rinsed  
with 3 X 4 ml of ice cold 10 mM Tris buffer (pH 7.4  
25 at room temperature). The filter discs are placed in 12 X 75 mM polypropylene tubes for counting on as Packard Multi-Prias gamma counter.

30

HUMAN HT-29 CELL MEMBRANE ASSAY

HT-29 cells were routinely grown in 225 cm<sup>2</sup> Costar tissue culture flasks at 37°C in a humidified atmosphere of 5% CO<sub>2</sub>/95% air in Dulbecco's modified Eagle's medium with high glucose containing 50 U/ml penicillin, 50 µg/ml streptomycin, 5% fetal bovine serum and 5% newborn calf serum. Cells were subcultured with 0.25% trypsin at a ratio of 1:6 with confluence being reached at 48 to 72 hrs. Cells from confluent flasks (approx.  $1 \times 10^8$  cells/flask) were harvested by scraping. The cells were pelleted by centrifugation (1000 x g, 5 min), resuspended in 50 mM Tris HCl, pH 7.4, and homogenized with a polytron (setting 7 for 10 sec.). Cell membranes were washed twice by centrifugation (50,000 x g, 15 min) and rehomogenization. The resulting pellet was either frozen at -70°C for future use or run directly in the assay by resuspending at a concentration of  $0.5 \times 10^6$  cells per 0.750 ml of assay buffer (50 mM Tris HCl, pH 7.4, containing 1 mM EDTA, 40 µg/ml bacitracin, 1 mM phenanthroline, 10 µg/ml soybean trypsin inhibitor and 100 µM phenylmethylsulfonyl fluoride).

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Assay tubes (13 x 100 polypropylene) receive 1) 100 µl buffer or 10 µM neurotensin (for non-specific binding) 2) 100 µl of 60 pM [<sup>125</sup>I]neurotensin 3) 20 µl test compounds 4) 750 µl cell membrane suspension and 5) enough buffer to bring final volume to 1 ml. After 30 minutes at room temperature, the samples are filtered using a Brandel M24 cell harvester with GF/B filtermats that have been presoaked in 0.2%

polyethyleneimine for 2 hours. The tubes are rinsed with 3 x 4 ml of ice cold 10 mM Tris buffer (pH 7.4 at room temperature). The filter discs are placed in 12 x 75 mM polypropylene tubes for counting on a Packard Multi-Prias gamma counter. [The above assay is derived from the assay described in Kitabgi, P. et al., Molecular Pharmacology, 18, 11-19 (1980)].

#### NEUROTENSIN BINDING ASSAY USING HUMAN FRONTAL CORTEX

10

Post-mortem human brain is obtained through the National Disease Research Interchange (Philadelphia, PA). The donors were without psychiatric or neurological abnormalities. Frontal cortex is dissected free of white matter and homogenized using a polytron in 20 volumes 50 mM Tris HCl, pH 7.4, and centrifuged at 50,000 x g for 20 min. The resulting pellet is washed twice by rehomogenization and centrifugation as before. The final pellet is resuspended at a concentration of 8 mg tissue (wet weight) per 0.750 ml of 50 mM Tris HCl, pH 7.4, which also contains 1 mM EDTA, 4 µg/ml bacitracin, 1 mM phenanthroline, 10 µg/ml soybean trypsin inhibitor and 100 µM phenyl methyl sulfonyl fluoride. Assay tubes (13 x 100 polypropylene) receive 1) 100 µl buffer or 10 µM neurotensin (for non-specific binding) 2) 100 µl of 60 pM [<sup>125</sup>I]neurotensin 3) 20 µl test compounds 4) 750 µl tissue suspension and 5) enough buffer to bring final volume to 1 ml. After 30 minutes at room temp, the samples are filtered using a Brandel M24 cell harvester with GF/B

filtermats that have been presoaked in 0.2% polyethyleneimine for 2 hours. The tubes are rinsed with 3 x 4 ml. of ice cold 10mM Tris buffer (pH 7.4 at room temperature). The filter discs are placed in 12 x 75 mM polypropylene tubes for counting on a  
5 Packard Multu-Prias gamma counter.

Using the methodology described above, representative compounds of the invention were evaluated and all were found to exhibit an activity of at least  $IC_{50} < 50 \mu M$  thereby demonstrating and  
10 confirming the utility of the compounds of the invention as effective neurotensin antagonists.

Typically, these combinations can be formulated into pharmaceutical compositions as discussed below.

15 About 1 to 100 mg. of compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as  
20 called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

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25 Illustrative of the adjuvants which can be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic  
30 acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the unit dosage

unitform is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated  
5 with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be  
10 formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a  
15 synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

The following examples further illustrate the preparation of the compounds of Formula I and  
20 their incorporation into pharmaceutical compositions and, as such, are not to be considered or construed as limiting the invention recited in the appended claims.

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25 3-n-Butyl-5-(4-chlorobenzylthio)-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-4H-1,2,4-triazole (Example 15)

30 3-n-Butyl-5-(4-chlorobenzylsulfinyl)-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole (Example 16)



3-n-Butyl-5-(4-chlorobenzylsulfonyl)-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole  
(Example 17)

5 3-n-Butyl-5-(4-nitrobenzylthio)-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole (Example 18)

10 3-n-Butyl-5-(4-nitrobenzylsulfinyl)-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole  
(Example 19)

15 3-n-Butyl-5-(cyclohexylmethylthio)-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole  
(Example 20)

3-n-Butyl-5-(4-chlorobenzylthio)-4-[4-[2-(1H-tetrazol-5-yl)benzamido]benzyl]-4H-1,2,4-triazole (Example 21)

20 3-n-Butyl-5-(4-chlorobenzylsulfinyl)-4-[4-[2-(1H-tetrazol-5-yl)benzamido]benzyl]-4H-1,2,4-triazole  
(Example 22)

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25 ~~3-n-Butyl-5-methylthio-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole (Example 22)~~

3-n-Butyl-5-methylsulfonyl-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole Example 24).

30 3-Benzyloxy-5-n-butyl-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole (Example 25)

3-(N-Benzyl-N-methylcarbamoyl)-5-n-butyl-4-[[2'-  
(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]-4H-1,2,4-  
triazole (Example 26)

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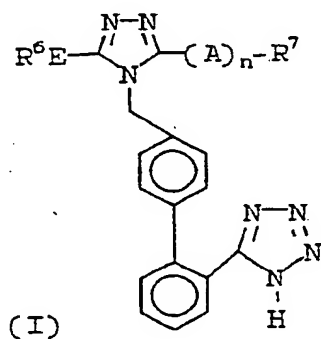
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EXAMPLES 77-92

The following compounds of formula (I) were prepared following the procedures of Examples 15-20 and 23-26 and Schemes 1-14, 17 and 18 in EP application 409,332.



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## Analysis

R <sup>d</sup> E	R <sup>7</sup> -(A) <sub>n</sub>	mp	formula	Analysis		
				C	H	N
77	n-Bu	107°C dec	C <sub>27</sub> H <sub>27</sub> N <sub>7</sub> S • 0.5H <sub>2</sub> O • 0.05CH <sub>2</sub> Cl <sub>2</sub>	calcd: 65.65 found: 65.64	5.72 5.64	19.82 19.54
78	n-Bu	84-85°C dec	C <sub>26</sub> H <sub>25</sub> N <sub>7</sub> S • 0.75H <sub>2</sub> O • 0.15CH <sub>2</sub> Cl <sub>2</sub>	calcd: 64.02 found: 64.30	5.50 5.50	20.03 19.72
79	n-Bu	79-80°C	C <sub>28</sub> H <sub>29</sub> N <sub>7</sub> S • 0.75H <sub>2</sub> O	calcd: 66.05 found: 66.32	6.04 5.92	19.26 19.16
80	n-Pr	90-92°C	C <sub>26</sub> H <sub>24</sub> ClN <sub>7</sub> S • 0.2H <sub>2</sub> O • 0.8CH <sub>3</sub> O (methanol)	calcd: 60.58 found: 60.65	5.24 5.15	18.46 18.10

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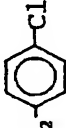
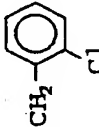
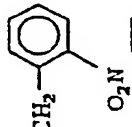
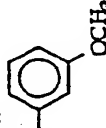
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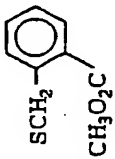
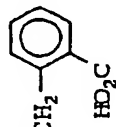
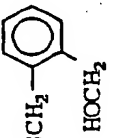
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## Analysis

R <sup>6</sup> E	R <sup>7</sup> -(A) <sub>n</sub>	mp	formula	C	H	N
81 n-Pentyl		97-99°C	C <sub>28</sub> H <sub>28</sub> ClN <sub>7</sub> S•0.75H <sub>2</sub> O	calcd: 61.86 found: 61.85	5.45 5.41	18.04 18.12
82 n-Bu		79-80°C	C <sub>27</sub> H <sub>26</sub> ClN <sub>7</sub> S•0.1CH <sub>2</sub> Cl <sub>2</sub>	calcd: 62.06 found: 62.34	5.03 5.24	18.70 18.58
83 n-Bu		115°C dec	C <sub>27</sub> H <sub>26</sub> N <sub>8</sub> O <sub>2</sub> S•0.75H <sub>2</sub> O	calcd: 60.03 found: 59.93	5.13 5.13	20.75 20.47
84 n-Bu		78-80°C	C <sub>28</sub> H <sub>29</sub> N <sub>7</sub> OS			

R <sup>6</sup> E	R <sup>7</sup> -(A) <sub>n</sub>	mp	Formula	Analysis		
				C	H	N
85	n-Bu SCH <sub>2</sub> - 	95-97°C	C <sub>28</sub> H <sub>29</sub> N <sub>7</sub> OS			
86	n-Bu SCH <sub>2</sub> - 	120-122°C dec	C <sub>29</sub> H <sub>29</sub> N <sub>7</sub> O <sub>2</sub> S • 1.5 H <sub>2</sub> O • 0.2 CH <sub>2</sub> Cl <sub>2</sub>	calcd: 59.62 found: 59.77	5.55 5.44	16.67 16.44
87	n-Bu SCH <sub>2</sub> - 	203-204°C dec	C <sub>28</sub> H <sub>27</sub> N <sub>7</sub> O <sub>2</sub> S			
88	n-Bu SCH <sub>2</sub> - 	93-95°C	C <sub>28</sub> H <sub>29</sub> N <sub>7</sub> OS • 0.3 H <sub>2</sub> O • 0.25 CH <sub>2</sub> Cl <sub>2</sub>	calcd: 63.03 found: 63.29	5.64 5.92	18.22 17.89

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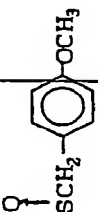

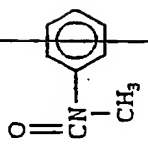
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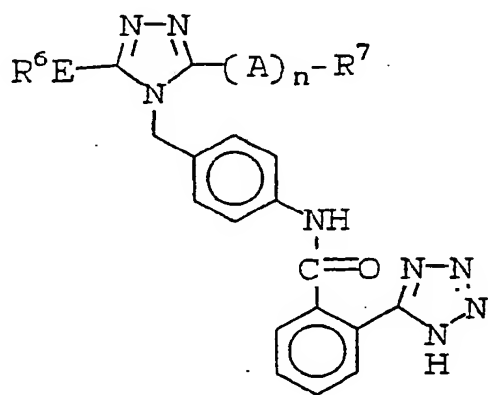
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## Analysis

R <sup>6</sup> E	R <sup>7</sup> -(A) <sub>n</sub> <sup>-</sup>	mp	Formula	Analysis		
				C	H	N
89	n-Bu SCH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	90-91°C	C <sub>24</sub> H <sub>29</sub> N <sub>7</sub> S • 0.15CH <sub>2</sub> Cl <sub>2</sub>	calcd: 63.00 found: 63.07	6.42 6.50	21.30 21.00
90	n-Bu SCH <sub>2</sub> - 	125-126°C	C <sub>28</sub> H <sub>29</sub> N <sub>7</sub> O <sub>2</sub> S			
91	n-Bu 	106-107°C	C <sub>21</sub> H <sub>23</sub> N <sub>7</sub> OS			
92	n-Bu 	100°C	C <sub>28</sub> H <sub>28</sub> N <sub>8</sub> O • 0.15CH <sub>2</sub> Cl <sub>2</sub>	calcd: 66.91 found: 67.27	5.65 5.90	22.18 21.82

EXAMPLES 93-108

The following compounds of formula (I) were  
or can be prepared following the procedure of  
Examples 21 and 22 and Schemes 1-15, 18 and 19.



(I)



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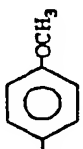
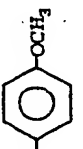


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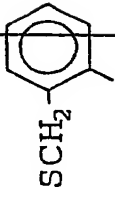
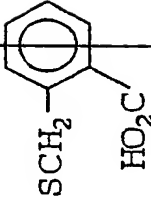
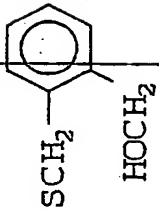
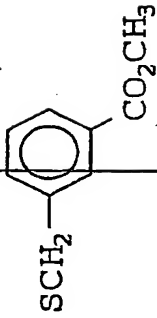
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## Analysis

R <sup>6</sup> E	R <sup>7</sup> (A) <sub>n</sub>	mp	Formula	Analysis		
				C	H	N
93	n-Bu 	130-132°C dec.	C <sub>29</sub> H <sub>30</sub> N <sub>8</sub> O <sub>2</sub> S • 0.5H <sub>2</sub> O	calcd: 61.79 found: 61.50	5.54 5.52	19.88 19.78
94	n-Bu 	135-137°C	C <sub>29</sub> H <sub>30</sub> N <sub>8</sub> O <sub>2</sub> S • 0.25H <sub>2</sub> O • 0.15C <sub>4</sub> H <sub>8</sub> O <sub>2</sub>	calcd: 60.42 found: 60.25	5.43 5.60	19.05 18.88
95	n-Bu 		(ethyl acetate)			
96	n-Bu 					

	R <sup>6</sup> E	R <sup>7</sup> -(A) <sub>n</sub> -	mp	formula	Analysis		
					C	H	N
97	n-Bu						
98	n-Bu						
99	n-Bu						
100	n-Bu						

5

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30

Analysis

N

H

C

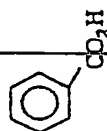
formula

mp

 $R^7-(A)_n$  $R^6E$ 

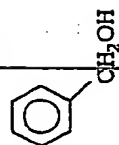
101

n-Bu

SCH<sub>2</sub>

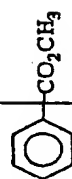
102

n-Bu

SCH<sub>2</sub>

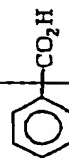
103





n-Bu

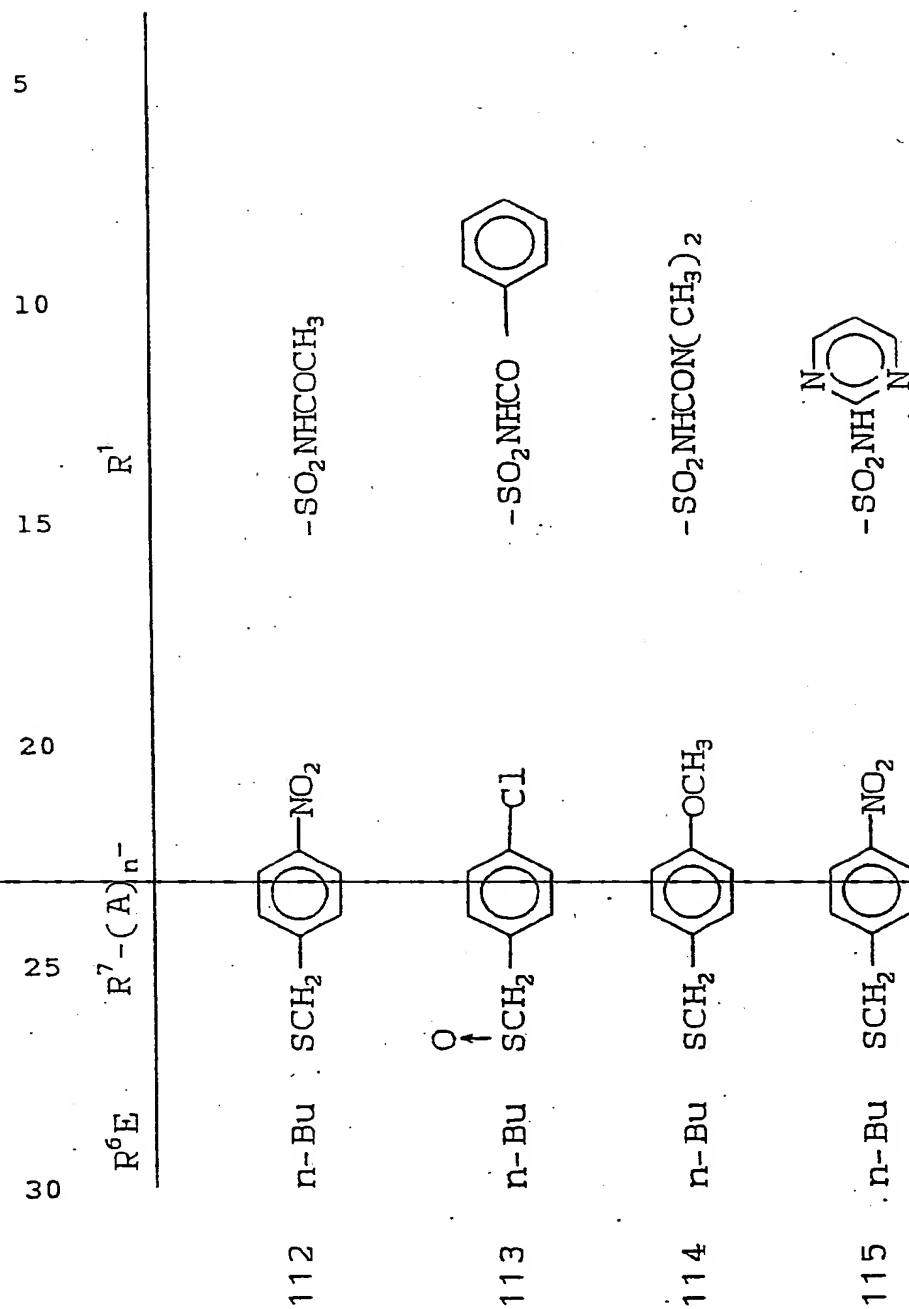
SCH<sub>2</sub>

104

n-Bu

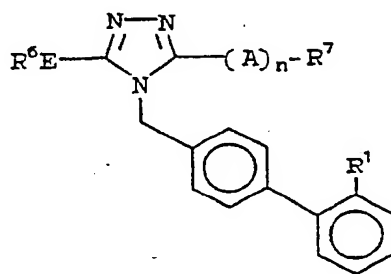
SCH<sub>2</sub>

	R <sup>6</sup> E	R <sup>7</sup> -(A) <sub>n</sub> -	mp	formula	Analysis		
					C	H	N
5							
10							
15							
20							
25							
30	n-Bu						
	n-Bu						
	n-Bu						
105							
106							
107							
108							



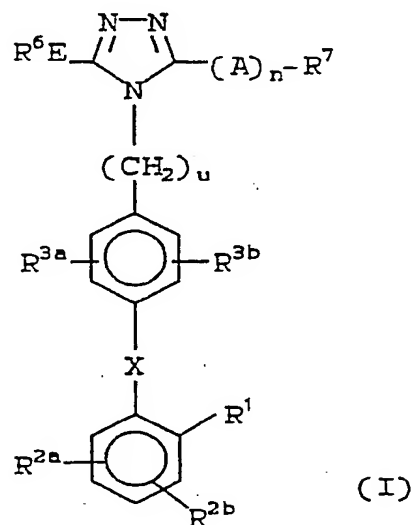
EXAMPLES 109-115

The following compounds of formula (I) can  
be prepared according to Schemes 20-22 (and earlier  
Schemes referred to therein).



WHAT IS CLAIMED IS:

1. A method of treating gastrointestinal disorders which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of structural formula:



or a pharmaceutically acceptable salt thereof,  
wherein:

25  $R^1$  is

- 30
- (a)  $-\text{NHSO}_2\text{R}^{23}$ ,
  - (b)  $-\text{NHSO}_2\text{NHCOR}^{23}$ ,
  - (c)  $-\text{NHCONHSO}_2\text{R}^{23}$ ,
  - (d)  $-\text{SO}_2\text{NHR}^{23}$ ,
  - (e)  $-\text{SO}_2-\text{NHCOR}^{23}$ ,
  - (f)  $-\text{SO}_2\text{NHCONR}^9\text{R}^{23}$ ,

- (g)  $-\text{SO}_2\text{NHCOOR}^{23}$ ,  
(h)  $-\text{SO}_2\text{NHOR}^{23}$ ,  
(i)  $-\text{CH}_2\text{SO}_2\text{NHCOR}^{23}$ ,  
(j)  $-\text{CH}_2\text{SO}_2\text{NHCONHR}^{23}$ ,  
5 (k)  $-\text{CO}_2\text{H}$ , or  
(l)  $-\text{1H-tetrazol-5-yl}$ ;

$\text{R}^{2a}$  and  $\text{R}^{2b}$  are each independently:

- (a) hydrogen,  
10 (b) Cl, Br, I, F,  
(c)  $\text{CF}_3$ ,  
(d)  $\text{C}_1\text{-C}_4\text{-alkyl}$ , or  
(e)  $\text{C}_1\text{-C}_4\text{-alkoxy}$ ;

15  $\text{R}^{3a}$  is

- (a) H,  
(b) Cl, Br, I, F,  
(c)  $\text{C}_1\text{-C}_6\text{-alkyl}$ ,  
(d)  $\text{C}_1\text{-C}_6\text{-alkoxy}$ , or  
20 (e)  $\text{C}_1\text{-C}_6\text{-alkoxy-C}_1\text{-C}_4\text{-alkyl}$ ;

$\text{R}^{3b}$  is

- (a) H,  
(b) Cl, Br, I, F,  
25 (c)  $\text{C}_1\text{-C}_6\text{-alkyl}$ ,  
(d)  $\text{C}_3\text{-C}_6\text{-cycloalkyl}$ ,  
(e)  $\text{C}_1\text{-C}_6\text{-alkoxy}$ , or  
(f)  $\text{CF}_3$ ;

30  $\text{R}^4$  is H,  $\text{C}_1\text{-C}_6$  alkyl, benzyl or phenyl;

$\text{R}^5$  is H or  $-\text{CH}(\text{R}^4)-\text{O}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{R}^4$ ;



E is a single bond,  $-\text{NR}^{13}(\text{CH}_2)_s-$ ,  $-\text{S}(\text{O})_x(\text{CH}_2)_s-$  where x is 0 to 2 and s is 0 to 5,  $-\text{CH}(\text{OH})-$ ,  $-\text{O}(\text{CH}_2)_s-$ ,  $-\text{CO}-$ ;

5 R<sup>6</sup> is

- (a) aryl, wherein aryl is defined as phenyl or naphthyl which can be unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of Cl, Br, I, F,  $-\text{O}-\text{C}_1-\text{C}_4\text{-alkyl}$ ,  $\text{C}_1-\text{C}_4\text{-alkyl}$ ,  $-\text{NO}_2$ ,  $-\text{CF}_3$ ,  $-\text{SO}_2\text{NR}^9\text{R}^{10}$ ,  $-\text{S}-\text{C}_1-\text{C}_4\text{-alkyl}$ ,  $-\text{OH}$ ,  $-\text{NH}_2$ ,  $\text{C}_3-\text{C}_7\text{-cycloalkyl}$ ,  $\text{C}_2-\text{C}_{10}\text{-alkenyl}$ ;
- 10 (b)  $\text{C}_1-\text{C}_6\text{-alkyl}$ ,  $\text{C}_2-\text{C}_6\text{-alkenyl}$  or  $\text{C}_2-\text{C}_6\text{-alkynyl}$  each of which can be optionally substituted with a substituent selected from the group consisting of aryl as defined above,  $-\text{O}-\text{C}_1-\text{C}_4\text{-alkyl}$ ,  $\text{C}_3-\text{C}_7\text{-cycloalkyl}$ , Cl, Br, I, F,  $-\text{OH}$ ,  $-\text{NH}_2$ ,  $-\text{NH}(\text{C}_1-\text{C}_4\text{-alkyl})$ ,  $-\text{N}(\text{C}_1-\text{C}_4\text{-alkyl})_2$ ,  $-\text{NH}-\text{SO}_2\text{R}^4$ ,  $-\text{COOR}^4$ ,  $-\text{SO}_2\text{NHR}^9$ ,  $-\text{S}-\text{C}_1-\text{C}_4\text{-alkyl}$ ;
- 15 (c) an unsubstituted, monosubstituted or disubstituted aromatic 5 or 6 membered ring which can contain one or two members
- 
- 25 selected from the group consisting of N, O, S, and wherein the substituents are members selected from the group consisting of  $-\text{OH}$ ,  $-\text{SH}$ ,  $\text{C}_1-\text{C}_4\text{-alkyl}$ ,  $\text{C}_1-\text{C}_4\text{-alkyloxy}$ ,  $-\text{CF}_3$ , Cl, Br, I, F, or  $\text{NO}_2$ ;
- (d) mono-, di-, tri- or perfluoro- $\text{C}_1-\text{C}_5\text{-alkyl}$ ;
- 30 (e)  $\text{C}_3-\text{C}_7\text{-cycloalkyl}$ , unsubstituted or substituted with one or more substituents selected from the group consisting of

- C<sub>1</sub>-C<sub>4</sub>-alkyl, -O-C<sub>1</sub>-C<sub>4</sub>-alkyl, -S-C<sub>1</sub>-C<sub>4</sub>-alkyl,  
-OH, perfluoro-C<sub>1</sub>-C<sub>4</sub>-alkyl or Cl, Br, F, I;  
(f) C<sub>3</sub>-C<sub>7</sub>-cycloalkyl-C<sub>1</sub>-C<sub>3</sub>-alkyl wherein the  
cycloalkyl is substituted as in (e) above;

5

A is S(O)<sub>p</sub>, -O- NHC(=O)-, -C(=O)NR<sup>13</sup>-, or -NR<sup>13</sup>-,  
wherein p is 0 to 2;

R<sup>7</sup> is

10

- (a) C<sub>1</sub>-C<sub>10</sub>-alkyl;  
(b) substituted C<sub>1</sub>-C<sub>10</sub> alkyl in which one or  
more substituent(s) is selected from

15

- (1) Cl, Br, I, F,  
(2) hydroxy,  
(3) C<sub>1</sub>-C<sub>10</sub>-alkoxy,  
(4) C<sub>1</sub>-C<sub>5</sub>-alkoxycarbonyl,  
(5) C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyloxy,  
(6) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,  
(7) phenyl,

20

- (8) substituted phenyl in which the  
substituents are V and W,  
(9) C<sub>1</sub>-C<sub>10</sub>-alkyl-S(O)<sub>p</sub>,  
(10) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-S(O)<sub>p</sub>,

25

- (11) phenyl-S(O)<sub>p</sub>,  
(12) substituted phenyl-S(O)<sub>p</sub> in which the  
substituents are V and W,  
(13) oxo,

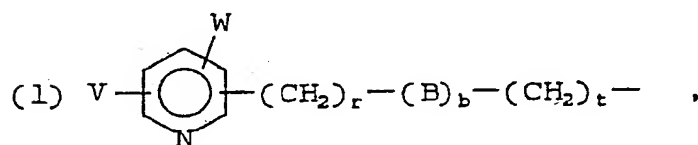
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- (14) carboxy,  
(15) NR<sup>9</sup>R<sup>10</sup>,  
(16) C<sub>1</sub>-C<sub>5</sub>-alkylaminocarbonyl,  
(17) di(C<sub>1</sub>-C<sub>5</sub>-alkyl)aminocarbonyl,  
(18) cyano;

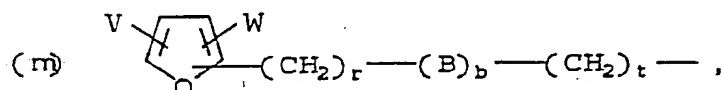
- (c) perfluoro-C<sub>1</sub>-C<sub>4</sub>-alkyl,  
(d) C<sub>2</sub>-C<sub>10</sub>-alkenyl,  
(e) C<sub>2</sub>-C<sub>10</sub>-alkynyl,  
(f) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,  
5 (g) substituted C<sub>3</sub>-C<sub>8</sub>-cycloalkyl in which one or  
more substituent(s) is selected from:  
(1) Cl, Br, I, F,  
(2) hydroxy,  
(3) C<sub>1</sub>-C<sub>10</sub>-alkoxy,  
10 (4) C<sub>1</sub>-C<sub>5</sub>-alkoxycarbonyl,  
(5) C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyloxy,  
(6) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,  
(7) phenyl,  
(8) substituted phenyl in which the  
15 substituents are V and W,  
(9) C<sub>1</sub>-C<sub>10</sub>-alkyl-S(0)<sub>p</sub> in which p is 0 to 2,  
(10) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-S(0)<sub>p</sub>,  
(11) phenyl-S(0)<sub>p</sub>,  
(12) substituted phenyl-S(0)<sub>p</sub> in which the  
20 substituents are V and W,  
(13) oxo,  
(14) carboxy,  
(15) ~~NR<sup>9</sup>R<sup>10</sup>~~,  
25 (16) C<sub>1</sub>-C<sub>5</sub>-alkylaminocarbonyl,  
(17) di(C<sub>1</sub>-C<sub>5</sub>-alkyl)aminocarbonyl,  
(18) cyano,  
(19) C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl;  
(20) (C<sub>1</sub>-C<sub>5</sub>) alkyl,  
(h) phenyl,  
30 (i) substituted phenyl in which the substituents  
are V and W,

- (j) phenyl-(CH<sub>2</sub>)<sub>r</sub>-(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>- ,  
 (k) substituted aryl-(CH<sub>2</sub>)<sub>r</sub>-(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>- in  
 which the phenyl group is substituted with V  
 and W;

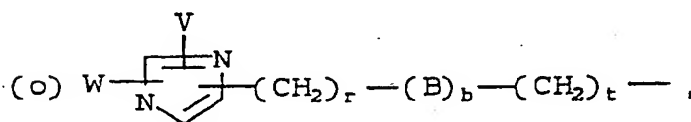
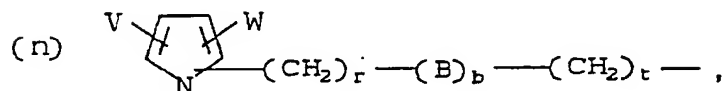
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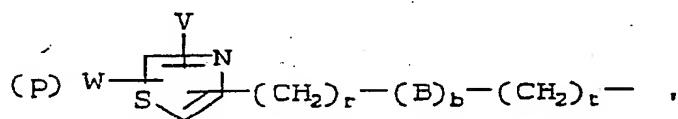
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25 with the proviso that when E is a single bond and n  
 is 0, then R<sup>7</sup> is:

- (a) substituted C<sub>1</sub>-C<sub>10</sub>-alkyl in which one or  
 more substituent(s) is selected from:

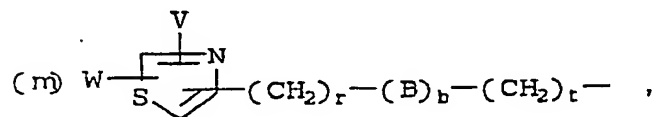
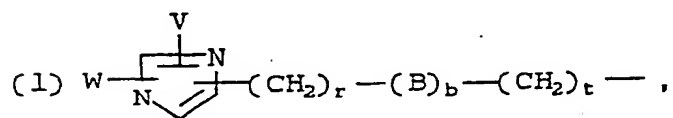
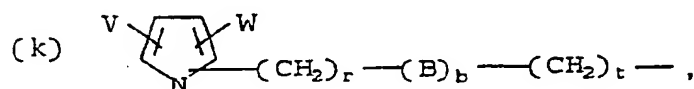
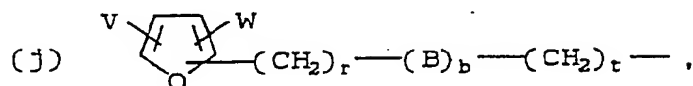
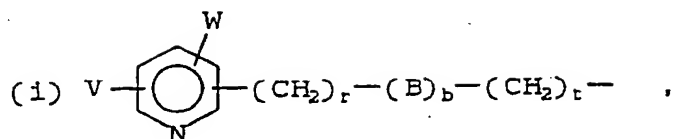
- (1) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,  
 (2) phenyl,

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- (3) substituted phenyl in which the substituents are V and W,
- (4)  $C_3-C_8$ -cycloalkyl-S(O)<sub>p</sub> where p is 0 to 2,
- 5 (5) phenyl-S(O)<sub>p</sub> where p is 0 to 2,
- (6) substituted phenyl-S(O)<sub>p</sub> where p is 0 to 2 and the substituents are V and W:
- (b) CF<sub>3</sub>;
- (c)  $C_3-C_8$ -cycloalkyl;
- 10 (d) substituted  $C_3-C_8$ -cycloalkyl in which the substituent is selected from:
- (1)  $C_1-C_5$ -alkyl,
- (2)  $C_1-C_5$ -alkoxy;
- (e) phenyl,
- 15 (f) substituted phenyl as defined above in which the substituents are V and W;
- (g) phenyl-(CH<sub>2</sub>)<sub>r</sub>-(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>- in which b is 0 when B is -C(O)-;
- 20 (h) substituted phenyl-(CH<sub>2</sub>)<sub>r</sub>-(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>- in which b is 0 when B is -C(O)- and the phenyl group is substituted with V and W;
- 

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30



n is 0 or 1;

B is  $-C(O)-$ ,  $-S-$ , or  $-O-$ ,  $-NR^4$ ,  $-NR^4C(O)-$ , or  $-C(O)NR^4$ ;

b is 0 or 1;

r and t are 0 to 2;

u is 1 or 2;

p is 0 to 2;

V and W are each independently selected from:

- (a) H,
- (b) C<sub>1</sub>-C<sub>5</sub>-alkoxy,
- (c) C<sub>1</sub>-C<sub>5</sub>-alkyl,
- 5 (d) hydroxy,
- (e) C<sub>1</sub>-C<sub>5</sub>-alkyl-S(O)<sub>p</sub>,
- (f) -CN,
- (g) -NO<sub>2</sub>,
- (h) -NR<sup>9</sup>R<sup>10</sup>;
- 10 (i) C<sub>1</sub>-C<sub>4</sub>-alkyl-CONR<sup>9</sup>R<sup>10</sup>,
- (j) -CO<sub>2</sub>R<sup>9</sup>,
- (k) C<sub>1</sub>-C<sub>5</sub>-alkyl-carbonyl,
- (l) trifluoromethyl,
- (m) Cl, Br, I, F,
- 15 (n) hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl,
- (o) C<sub>1</sub>-C<sub>4</sub>-alkyl-CO<sub>2</sub>R<sup>9</sup>,
- (p) -1H-tetrazol-5-yl,
- (q) -NHSO<sub>2</sub>CF<sub>3</sub>,
- (r) aryl,
- 20 (s) -OCONR<sup>9</sup>R<sup>10</sup>,
- (t) -NR<sup>4</sup>CO<sub>2</sub>R<sup>9</sup>,
- (u) -NR<sup>4</sup>CONR<sup>9</sup>R<sup>10</sup>,
- ~~(v) -NR<sup>4</sup>CON(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>Q where Q is O, S(O)<sub>p</sub> or NR<sup>9</sup>,~~
- (w) -OCON(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>Q, or
- 25 (x) -CONR<sup>9</sup>R<sup>10</sup>;

R<sup>9</sup> is H, C<sub>1</sub>-C<sub>5</sub>-alkyl, phenyl or benzyl;

R<sup>10</sup> is H, C<sub>1</sub>-C<sub>4</sub>-alkyl; or,

R<sup>9</sup> and R<sup>10</sup> together may be -(CH<sub>2</sub>)<sub>m</sub>- where m is 3-6;

R<sup>11</sup> is H, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>4</sub>-alkenyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, or -CH<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>R<sup>20</sup>;

R<sup>12</sup> is -CN, -NO<sub>2</sub> or -CO<sub>2</sub>R<sup>4</sup>;

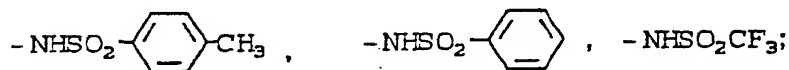
R<sup>13</sup> is H, C<sub>1</sub>-C<sub>4</sub>-acyl, C<sub>1</sub>-C<sub>6</sub>-alkyl, allyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, phenyl or benzyl;

R<sup>14</sup> is H, C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-perfluoroalkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, phenyl or benzyl;

R<sup>15</sup> is H, C<sub>1</sub>-C<sub>6</sub>-alkyl, hydroxy;

R<sup>16</sup> is H, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, phenyl or benzyl;

R<sup>17</sup> is -NR<sup>9</sup>R<sup>10</sup>, -OR<sup>10</sup>, -NHCONH<sub>2</sub>, -NHCSNH<sub>2</sub>,



R<sup>18</sup> and R<sup>19</sup> are independently C<sub>1</sub>-C<sub>4</sub>-alkyl or taken together are -(CH<sub>2</sub>)<sub>q</sub>- where q is 2 or 3;

R<sup>20</sup> is H, -NO<sub>2</sub>, -NH<sub>2</sub>, -OH or -OCH<sub>3</sub>;

R<sup>21</sup> is C<sub>1</sub>-C<sub>5</sub> alkyl or CF<sub>3</sub>;



R<sup>22</sup> is

- 5 (a) phenyl, unsubstituted or substituted with 1  
or 2 substituents selected from the group  
consisting of: Cl, Br, I, or F, -O-C<sub>1</sub>-C<sub>4</sub>-  
alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyl, -NO<sub>2</sub>, -CF<sub>3</sub>, -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>,  
-S-C<sub>1</sub>-C<sub>4</sub>-alkyl, -OH, -NH<sub>2</sub>, -COOR<sup>4</sup>,  
C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, and C<sub>3</sub>-C<sub>10</sub>-alkenyl;
- 10 (b) C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl  
each of which is unsubstituted or  
substituted with one or more substituents  
selected from the group consisting of aryl,  
C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, Cl, Br, I, F, -OH,  
-O-C<sub>1</sub>-C<sub>4</sub>-alkyl, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub>-alkyl),  
-N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, -NH-SO<sub>2</sub>R<sup>4</sup>, -COOR<sup>4</sup>,  
15 -SO<sub>2</sub>NHR<sup>9</sup>, and -S-C<sub>1</sub>-C<sub>4</sub>-alkyl;
- (c) an unsubstituted, monosubstituted or  
disubstituted aromatic 5 or 6 membered ring  
comprising one or two heteroatoms selected  
from the group consisting of N, O, and S,  
20 and wherein the substituents are members  
selected from the group consisting of: -OH,  
-SH, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyloxy, -CF<sub>3</sub>,  
-COOR<sup>4</sup>, Cl, Br, I, F, and NO<sub>2</sub>; or
- 
- 25 (d) C<sub>3</sub>-C<sub>7</sub>-cycloalkyl unsubstituted or  
substituted with one or more substituents  
selected from the group consisting of:  
C<sub>1</sub>-C<sub>4</sub>-alkyl, -O-C<sub>1</sub>-C<sub>4</sub>-alkyl, -S-C<sub>1</sub>-C<sub>4</sub>-alkyl,  
-OH, -COOR<sup>4</sup>, C<sub>1</sub>-C<sub>4</sub>-perfluoroalkyl, Cl, Br,  
F, and I, or
- 30 (e) (C<sub>1</sub>-C<sub>4</sub>)-perfluoroalkyl;

R<sup>23</sup> is

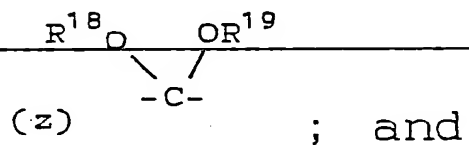
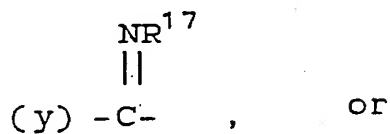
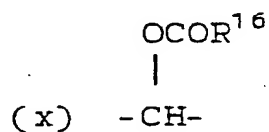
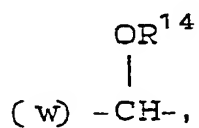
- (a) aryl,  
(b) heteroaryl,  
(c) C<sub>3</sub>-C<sub>7</sub>-cycloalkyl,  
5 (d) C<sub>1</sub>-C<sub>4</sub>-alkyl unsubstituted or substituted  
with a substituent selected from the group  
consisting of aryl, heteroaryl, -OH, -SH,  
C<sub>1</sub>-C<sub>4</sub>-alkyl, -O(C<sub>1</sub>-C<sub>4</sub>-alkyl),  
-S(C<sub>1</sub>-C<sub>4</sub>-alkyl), -CF<sub>3</sub>, Cl, Br, F, I, -NO<sub>2</sub>,  
10 -CO<sub>2</sub>H, -CO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub>-alkyl, -NH<sub>2</sub>,  
-NH(C<sub>1</sub>-C<sub>4</sub>-alkyl), -N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>,  
-N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>L where L is a single bond, CH<sub>2</sub>,  
O, S(O)<sub>p</sub> or NR<sup>9</sup>, -PO<sub>3</sub>H,  
-PO(OH)(O-C<sub>1</sub>-C<sub>4</sub>-alkyl);

15 X is

- (a) a carbon-carbon single bond,  
(b) -CO-,  
(c) -O-,  
(d) -S-,  
20 (e)  $\begin{array}{c} \text{-N-} \\ | \\ \text{R}^{13} \end{array}$ ,  
(f)  $\begin{array}{c} \text{-CON-} \\ | \\ \text{R}^{15} \end{array}$

- 
- 25 (g)  $\begin{array}{c} \text{-NCO-} \\ | \\ \text{R}^{15} \end{array}$ ,  
(h) -OCH<sub>2</sub>-,  
(i) -CH<sub>2</sub>O-,  
(j) -SCH<sub>2</sub>-,  
(k) -CH<sub>2</sub>S-,  
30 (l) -NHC(R<sup>9</sup>)(R<sup>10</sup>)-,  
(m) -NR<sup>9</sup>SO<sub>2</sub>-,  
(n) -SO<sub>2</sub>NR<sup>9</sup>-,

- (o)  $-\text{C}(\text{R}^9)(\text{R}^{10})\text{NH}-$ ,  
 (p)  $-\text{CH}=\text{CH}-$ ,  
 (q)  $-\text{CF}=\text{CF}-$ ,  
 (r)  $-\text{CH}=\text{CF}-$ ,  
 5 (s)  $-\text{CF}=\text{CH}-$ ,  
 (t)  $-\text{CH}_2\text{CH}_2-$ ,  
 (u)  $-\text{CF}_2\text{CF}_2-$ ,  
 (v) 1,1 and 1,2-disubstituted cyclopropyl,



30  
 Z is O,  $\text{NR}^{13}$  or S.

## 2. The method of Claim 1 wherein:

R<sup>1</sup> is:

- 5 (a) -SO<sub>2</sub>NHCOR<sup>23</sup>,  
(b) -SO<sub>2</sub>NHCONR<sup>9</sup>R<sup>23</sup>,  
(c) -SO<sub>2</sub>NHCOOR<sup>23</sup>,  
(d) -SO<sub>2</sub>NHOR<sup>23</sup>,  
(e) -CH<sub>2</sub>SO<sub>2</sub>NHCOR<sup>23</sup>, or  
10 (f) -1H-tetrazol-5-yl;

R<sup>2a</sup> is H;

R<sup>2b</sup> is H, F, Cl, CF<sub>3</sub> or C<sub>1</sub>-C<sub>4</sub>-alkyl;

15 R<sup>3a</sup> is H;

R<sup>3b</sup> is H, F, Cl, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>5</sub>-C<sub>6</sub>-cycloalkyl,  
-COOCH<sub>3</sub>, -COOC<sub>2</sub>H<sub>5</sub>, -SO<sub>2</sub>-CH<sub>3</sub>, NH<sub>2</sub>, -N(C<sub>1</sub>-C<sub>4</sub>-  
20 alkyl)<sub>2</sub> or -NH-SO<sub>2</sub>CH<sub>3</sub>;

E is a single bond, -O- or -S-;

R<sup>6</sup> is

- 25 (a) C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted  
with a substituent selected from the group  
consisting of Cl, CF<sub>3</sub>, OH, -O-CH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>,  
-S-CH<sub>3</sub>, -S-C<sub>2</sub>H<sub>5</sub> or phenyl;  
(b) C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl;  
(c) aryl unsubstituted or substituted with a  
30 substituent selected from the group  
consisting of Cl, F, Br, I, -CF<sub>3</sub>, -NO<sub>2</sub>, -OH,  
-NH<sub>2</sub>, -S-CH<sub>3</sub>, -S-C<sub>2</sub>H<sub>5</sub>, -SO<sub>2</sub>NH<sub>2</sub> -O-CH<sub>3</sub>;

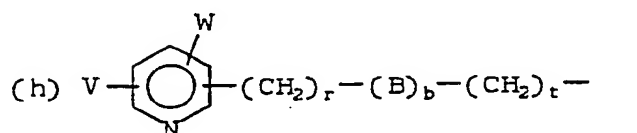
- (d) a heteroaryl selected from the group consisting of: 2-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, imidazolyl, thiazolyl, thienyl, or furyl;
- 5 (e) perfluoro-C<sub>1</sub>-C<sub>4</sub>-alkyl selected from CF<sub>3</sub>, CF<sub>3</sub>CF<sub>2</sub>, CF<sub>3</sub>CF<sub>2</sub>CF<sub>2</sub>, CF<sub>3</sub>CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>;
- (f) C<sub>3</sub>-C<sub>7</sub>-cycloalkyl unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF<sub>3</sub>, OH, -O-CH<sub>3</sub>, -OC<sub>2</sub>H<sub>5</sub>, -S-CH<sub>3</sub>, -S-C<sub>2</sub>H<sub>5</sub>, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, (CF<sub>2</sub>)<sub>2</sub>CF<sub>3</sub> or phenyl;
- 10

R<sup>7</sup> is:

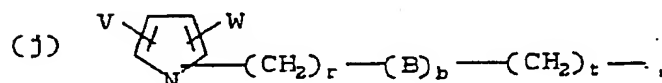
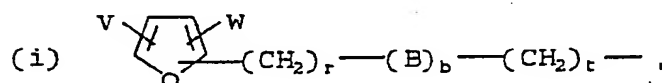
- (a) C<sub>1</sub>-C<sub>10</sub>-alkyl,
- 15 (b) substituted C<sub>1</sub>-C<sub>10</sub> alkyl in which one or two substituents are selected from:
- (1) hydroxy,
- (2) C<sub>1</sub>-C<sub>5</sub>-alkoxy,
- (3) C<sub>1</sub>-C<sub>5</sub>-alkoxycarbonyl,
- 20 (4) C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyloxy,
- (5) C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,
- (6) phenyl,
- 
- (7) substituted phenyl in which the substituents are V and W,
- 25 (8) C<sub>1</sub>-C<sub>5</sub>-alkyl-S(O)<sub>p</sub>
- (9) phenyl-S(O)<sub>p</sub>
- (10) substituted phenyl S(O)<sub>p</sub> in which the substituents are V and W,
- (11) oxo,
- 30 (12) carboxy,

- (13)  $C_1$ - $C_5$ -alkylaminocarbonyl,  
 (14) di( $C_1$ - $C_5$ -alkyl)aminocarbonyl;  
 (c)  $CF_3$ ,  
 (d) phenyl,  
 5 (e) substituted phenyl in which the substituents  
 are V and W,  
 (f) phenyl- $(CH_2)_r$ -(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>-,  
 (g) substituted phenyl- $(CH_2)_r$ -(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>-,

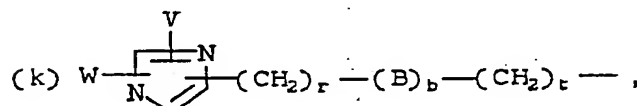
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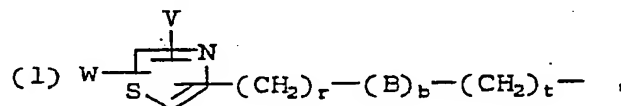
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A is -S-, -S(O)- or -O-;

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V and W are independently selected from:

- (a) hydrogen,
- (b) C<sub>1</sub>-C<sub>5</sub>-alkoxy,
- (c) C<sub>1</sub>-C<sub>5</sub>-alkyl,
- 5 (d) hydroxy,
- (e) NR<sup>9</sup>R<sup>10</sup>,
- (f) CO<sub>2</sub>R<sup>9</sup>,
- (g) trifluoromethyl,
- (h) Cl, Br, I, F,
- 10 (i) hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl-,
- (j) -1H-tetrazol-5-yl,
- (k) -NHSO<sub>2</sub>CF<sub>3</sub>,
- (l) C<sub>1</sub>-C<sub>5</sub>-alkyl-S(O)<sub>p</sub>-,
- (m) -CN,
- 15 (n) -NO<sub>2</sub>,
- (o) C<sub>1</sub>-C<sub>4</sub>-alkyl-CONR<sup>9</sup>R<sup>10</sup>,
- (p) C<sub>1</sub>-C<sub>5</sub>-alkylcarbonyl, or
- (q) -CONR<sup>9</sup>R<sup>10</sup>;

20 u is 1; and

X is:

- (a) carbon-carbon single bond,
- (b) -C(O)-,
- 25 (c) -NR<sup>15</sup>C(O)-.

3. The method of Claim 2 wherein:

30 E is a single bond or -S-;

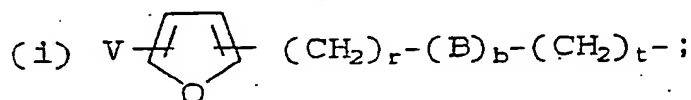
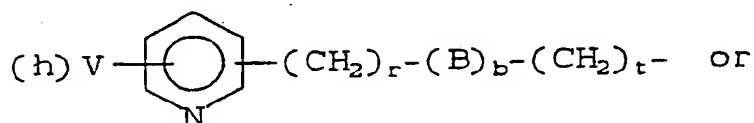
R<sup>2a</sup>, R<sup>2b</sup>, R<sup>3a</sup> and R<sup>3b</sup> are each H; and

R<sup>6</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl.

4. The method of Claim 3 wherein:

R<sup>7</sup> is:

- (a) C<sub>1</sub>-C<sub>10</sub>-alkyl,
- (b) substituted C<sub>1</sub>-C<sub>10</sub>-alkyl in which one or two  
5 substituents are selected from:
  - (1) hydroxy,
  - (2) C<sub>1</sub>-C<sub>5</sub>-alkoxy,
  - (3) C<sub>1</sub>-C<sub>5</sub>-alkoxycarbonyl,
  - (4) phenyl,
  - 10 (5) carboxy,
  - (6) C<sub>1</sub>-C<sub>5</sub>-alkylaminocarbonyl;
- (c) CF<sub>3</sub>,
- (d) phenyl,
- (e) phenyl substituted with V and W,
- 15 (f) phenyl-(CH<sub>2</sub>)<sub>r</sub>-(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>-,
- (g) phenyl-(CH<sub>2</sub>)<sub>r</sub>-(B)<sub>b</sub>-(CH<sub>2</sub>)<sub>t</sub>- in which the  
phenyl is substituted with V and W,



30 V and W are selected from:

- (a) hydrogen,
- (b) C<sub>1</sub>-C<sub>5</sub>-alkyl,
- (c) C<sub>1</sub>-C<sub>5</sub>-alkoxy,
- (d) CO<sub>2</sub>R<sup>9</sup>,



- (e) halogen,
- (f) hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl-,
- (g) -1H-tetrazol-5-yl-,
- (h) -NHSO<sub>2</sub>CF<sub>3</sub>,
- 5 (i) -CN,
- (j) -NO<sub>2</sub>; and

X is -NR<sup>15</sup>C(O)-, or a carbon-carbon single bond.

10           5.    The method of Claim 1 wherein the gastrointestinal disorder is selected from the group consisting of gastroesophagal reflux disorder (GERD), irritable bowel syndrome, diarrhea, cholic, ulcer, GI  
15 tumors, dyspepsia, pancreatitis, esophagitis and gastroparesis.

          6.    A pharmaceutical composition useful in the treatment of gastrointestinal disorders which comprises a pharmaceutically acceptable carrier and a  
20 pharmaceutically effective amount of a compound as recited in Claim 1.

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          7.    The method of Claim 1 wherein the  
25 central nervous system disorder is selected from the group consisting of: psychoses, depression, cognitive dysfunction, anxiety, tardive dyskinesia, drug dependency, panic attack and mania.

          8.    A pharmaceutical composition useful in  
30 the treatment of central nervous system disorders which comprises a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound as recited in Claim 1.

9. The use of a compound of the formula I as  
5 defined in any of claims 1 to 4 for the treatment of a  
disorder as defined in any of claims 1, 5 or 7.

Patents Act 1977

Examiner's report to the Comptroller under  
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Relevant Technical fields

(i) UK Cl (Edition L ) A5B (BHA BJA)

(ii) Int Cl (Edition 5 ) A61K 31/41

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASE: CAS-ONLINE

Search Examiner

J F JENKINS

Date of Search

26 APRIL 1993

Documents considered relevant following a search in respect of claims 1 TO 9

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
X	EP 0409332 A2 (MERCK) see Claims 5 and 7	6 and 8
X	US 5015651 (DU PONT) see column 4 line 60 to column 7 line 20 Examples 67-169, column 80 line 24 to column 82 line 8 & EP 0323841 A2	6 and 8
PA	US 5155126 (DU PONT) see Claim 1	1

SF2(p)

HCS - doc99\fil001151

Category	Identity of document and relevant passages	Relevant to claim(s)

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&: Member of the same patent family, corresponding document.

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